Original Research Article

Serum adenosine deaminase activity as a diagnostic biomarker in systemic lupus erythematosus patients

Abstract:

Background: Adenosine deaminase (ADA) is linked to the development of autoimmune diseases. In order to assess the use of serum ADA activity in diagnosing SLE and assessing disease activity, we examined the serum ADA activity of 70 SLE patients (35 active patients and 35 inactive patients) and 15 healthy controls.

Aim: The purpose of this paper is to evaluate the importance of serum ADA activities in identifying SLE and its connection to the activity of the illness.

Subjects and Methods: This a randomized prospective efficacy-controlled study conducted on 85 adult Patients (≥ 18 years) with clinically active SLE and clinically non-active SLE and carried at Clinical Pathology Department at Tanta University Hospital.

Results: In SLE patients, serum ADA activity was substantially higher in the active patients group than in the inactive patients group when compared to the control group. The best cut-off value for utilizing blood ADA activity to diagnose SLE patients was 12.8 U/L, according to a receiver operating characteristic curve analysis (ROC) (specificity, 100 percent; sensitivity, 100 percent). For lupus patients, serum ADA activity was shown to be more useful than other conventional hematological indicators such as complement C3, complement C4, ANA, and anti-ds DNA. Adenosine deaminase levels were also linked to ESR, blood urea, serum creatinine, Hb levels, Urine albumin/creatinine ratio, anti-nuclear antibody titre, anti-dsDNA antibody, total platelet count, complement C3 and complement C4 levels.

Conclusion: Serum ADA activity might be a possible diagnostic sign for SLE, and assessing serum ADA activity can help with illness evaluation and monitoring.

Keywords: Serum adenosine deaminase, systemic lupus erythematosus patients

Introduction:

Systemic lupus erythematosus (SLE) is one of the autoimmune disorders which target various body organs. There are different features of clinical findings in lupus disease varying from mild arthritis up to pericarditis, nephritis and neuropsychiatric manifestations and it has a course with durations of both remissions and relapses [(1)].

The prevalence of SLE worldwide is 14.6 to 50.8 cases per 100,000 with higher incidence in women at childbearing periods especially in the age of 15 to 45 years. SLE is manifested by excessive damage of cells and tissues by immune mediators and auto antibodies formation. In SLE disease the exact pathological mechanisms are still vague and it could be due to different factors, including genes, sex, environmental factors, drugs and infections. Also, the disease affects the life quality especially employment, psychological physical, and social functioning aspects. [(2,3)]

SLE patients are frequently report nonspecific constitutional manifestations like malaise, fever, fatigue, anorexia, weight loss, alopecia, arthralgia and other findings of diffuse generalized inflammation involving lymphadenopathy and hepatosplenomegaly. Skin symptoms in SLE are also denoted like the malar and butterfly rash, which is a SLE landmark, this rash is seen in 60 - 85% of patients, also discoid rash which is a common sign in SLE. [(1)]

Measuring SLE activity in patients was evaluated with the use of the lupus patient activity index (SLEDAI). Categories of activity have been determined according to the SLEDAI scores: (SLEDAI=0) no activity, (SLEDAI=1 to 5) mild activity, (SLEDAI=6 to 10) moderate activity, (SLEDAI=11 to 19) high activity and (SLEDAI≥20) extremely high activity [(4)].

Adenosine deaminase (ADA) is the adenosine hydrolytic enzyme and is extensively spread across a range of different tissues. The ADA has a major function for the immune system has been shown. Accumulated data has shown its essential involvement in immunologic response

function, development and maintenance. [5]

Subjects and Methods:

Subjects: The current research was conducted at the Clinical Pathology Department of Tanta University Hospital.

Study design: Randomized prospective efficacy-controlled study.

Study subjects: Adult Patients (≥ 18 years) with clinically active SLE and clinically non-active SLE.

Sample size:

- Group (1): 15 Healthy subjects as a control group.
- Group (2): 35 patients with clinically active SLE (SLEDAI score ≥ 6).
- Group (3): 35 patients with clinically non-active SLE (SLEDAI<6).

All patients and control subjects were gender and age matched to time of the present study.

Inclusion criteria:

Adult Patients aged eighteen years old or more, of any gender and diagnosed of SLE, having 4 or more criteria from the following 11 criteria whether in the clinically active state or in non- clinically active state according to (SLEDAI) [6] and the criteria are:

- Malar rash.
- Discoid rash.
- Photosensitivity.
- Oral ulcer.
- Non-erosive arthritis including 2 or more peripheral joints.
- Pleuritis or pericarditis.
- Renal illness as persistent proteinuria or urinary casts.
- Neurologic disorder whether psychosis or seizures.
- Hematological illness whether leucopenia or hemolytic anemia lower than 4,000/mm^3 or lymphopenia lower than 1,500/ mm^3 or thrombocytopenia lower than 100,000/ mm^3.
- Immunologic disorder as anti –DNA or anti- phospholipid antibodies.
- Positive antinuclear antibodies.

As confirmed by laboratory investigations.

Normal controls inclusion criteria:

A normal seeming healthy person who has no current or past record of SLE, or acute or chronic medical illness, signs or symptoms.

Exclusion criteria:

Patients not diagnosed of SLE, other autoimmune disease, diabetes mellitus patients and pregnant women.

ALL subjects were required to present:

1. Filling a complete history report.
2. Form a complete clinical examination.
3. Conduct laboratory investigations.

Statistical Analysis

The gathered data have been arranged by use of SPSS program, tabs and statistical analyses (Statistical Package for Social Sciences, version 19, SPSS Inc. Chicago, IL, USA).

Results:

Table (1): CBC findings among the studied groups

Variables	The studied subjects (n=85)		
	Control group	Patients with clinically active SLE	Patients with clinically non-active

	(n=15) (I)	(n=35) (II)	SLE (n=35) (III)
•CBC results:			
-Hb (g/dl):			
Range Mean±SD	12.10-13.70 12.91±0.50	7.00-9.60 8.19±0.76	10.20-12.00 11.04±0.60
F value P	307.89 0.0001*		
Scheffe test P	I vs II, P=0.0001* I vs III, P=0.0001* II vs III, P=0.0001*		
-TLC (*1000/mm^3):			
Range Mean±SD	4-6 5.08±0.61	3-6.2 4.86 ±0.97	4-6.8 5.17±0.81
F value P	1.211 0.303		
Scheffe test P	I vs II, P=0.424 I vs III, P=0.694 II vs III, P= 0.146		
-Total platelet count (*1000/mm^3):			
Range Mean±SD	153-221 180.64±21.88	102-156 124.94±25.13	108-144 133±9.42
F value P	41.445 0.0001*		
Scheffe test P	I vs II, P=0.0001* I vs III, P=0.0001* II vs III, P=0.601		

*Significant (P<0.05)

Table (1) shows comparison between the studied groups as regard to CBC findings. Hb concentration ranged from {12.10-13.70, 7 -9.60, 10.20-12 (g/dl)} with a mean value of {12.91±0.50, 8.19±0.76, 11.04±0.60} in control group (I), clinically active SLE group (II) and clinically non- active SLE group (III) respectively. In Hb concentration, the research detected statistically significant lessening in both active and non-active SLE groups in comparison to the control group. Moreover, a statistically significant decline of Hb concentration in active SLE was documented when contrasted with non-active SLE group, P=0.0001.

TLC ranged from {4-6, 3-6.2, 4-6.8 (1000/mm3)} with a mean value of {5.08±0.61, 4.86 ±0.97, 5.17±0.81} in control group (I), clinically active SLE group (II) and clinically non-active SLE group (III) respectively. No statistically significant decrease of TLC for active SLE group was found when contrasted with control group, P=0.424 also no significant variation was discovered among the non-active SLE group and control group, P=0.694 and no significant variation was discovered among the active SLE group and non-active SLE group, P=0.146.

Platelet's count ranged from {153-221, 102-156, 108-144 (1000/mm3)} with a mean value of {180.64±21.88, 124.94±25.13, 133±9.42} in control group (I), clinically active SLE group (II) and clinically non-active SLE group (III) respectively. We found statistically significant reduction of platelets count in active SLE group in comparison to the control group, P=0.0001, and a statistically significant decline of platelets count was discovered in the non-active SLE group in comparison to the control group, P=0.0001 and no significant variation was discovered among both the active SLE group and non- active SLE group, P=0.601.

Table (2): Renal function results among the studied groups

Variables	The studied subjects (n=85)

	Control group (n=15) (I)	Patients with clinically active SLE (n=35) (II)	Patients with clinically non-active SLE (n=35) (III)
•Renal function investigation results:			
-Blood urea (mg/dl):			
Range Mean±SD	24-40 31±4.84	51-78 63.77±8.33	34-53 43.63±6.03
F value P	140.61 0.0001*		
Scheffe test P	I vs II, P=0.0001* I vs III, P=0.0001* II vs III, P=0.0001*		
-Serum creatinine (mg/dl):			
Range Mean±SD	0.82-1.31 1.03±0.17	2.79-4.53 3.71±0.56	1.49-2.52 2.01±0.33
F value P	257.66 0.0001*		
Scheffe test P	I vs II, P=0.0001* I vs III, P=0.0001* II vs III, P=0.0001*		
-Urine albumin / creatinine ratio(mg/g):			
Range Mean±SD	15-26 20±3.85	263-418 341.46±49.90	131-227 178.09±31.09
F value P	404.048 0.0001*		
Scheffe test P	I vs II, P=0.0001* I vs III, P=0.0001* II vs III, P=0.0001*		

*Significant (P<0.05).

Table (2) shows contrast among the studied groups as regard to renal functions. Blood urea ranged from {24-40, 51-78, 34-53 (mg/dl)} with a mean value of {31±4.84, 63.77±8.33, 43.63±6.03} in control group (I), clinically active SLE group (II) and clinically non-active SLE group (III) respectively. Moreover, statistically significant increase of blood urea in active SLE group when contrasted with the control group, P=0.0001, as well as a significant increase of blood urea in non -active SLE group at contrasting with the control group P=0.0001 and there is significant increase of blood urea in active SLE group in comparison to non -active SLE group, P=0.0001.

Serum creatinine ranged from {0.82-1.31,2.79-4.53,1.49-2.52 (mg/dl)} with a mean value of {1.03±0.17, 3.71±0.56, 2.01±0.33} in control group (I), clinically active SLE group (II) and clinically non-active SLE group (III) respectively. Regarding serum creatinine, statistically significant increase was discovered in active SLE group in comparison to control group, P=0.0001, and a significant increase of serum creatinine in non- active SLE group was found in comparison to control group, P=0.0001 and a significant increase of serum creatinine in active SLE group was found when contrasted with non-active SLE group, P=0.0001.

Urine albumin /creatinine ratio ranged from {15-26, 263-418,131-227 (mg/g)} with a mean value of {20±3.85, 341.46±49.90, 178.09±31.09} in control group (I), clinically active SLE group (II) and clinically non-active SLE group (III) respectively. And a statistically significant rise of urine albumin/creatinine ratio in active SLE group was found in contrast with the control group, P=0.0001 and a significant increase of urine albumin/creatinine ratio in non- active SLE group was detected in contrast with the control group, P=0.0001 and a significant increase of urine albumin /creatinine ratio in active SLE group was found in comparison to non- active SLE group, P=0.0001.

Table (3): Specific laboratory investigation results among the studied patients with SLE (clinically active and inactive) and the control group (n=85)

Variables	The studied subjects (n=85)		
	Control group (n=15) (I)	Patients with clinically active SLE (n=35) (II)	Patients with clinically non-active SLE (n=35) (III)
•Specific laboratory investigation results:			
-Anti-ds DNA antibody (IU/ml):			
Range Mean±SD	33-58 46.76±7.93	230-370 299.37±44.3	150-235 194.17±27.65
F value P	301.488 0.0001*		
Scheffe test P	I vs II, P=0.0001* I vs III, P=0.0001* II vs III, P=0.0001*		
-Complement C3 (mg/dl):			
Range Mean±SD	144-175 156.80±9.66	12-43 27.03±9.49	62-90 74.83±8.51
F value P	1070.83 0.0001*		
Scheffe test P	I vs II, P=0.0001* I vs III, P=0.0001* II vs III, P=0.0001*		
-Complement C4 (mg/dl):			
Range Mean±SD	33-50 39.73±5.16	5-12 8.17±2.15	6-13 9.29±2.14
F value P	712.01 0.0001*		
Scheffe test P	I vs II, P=0.0001* I vs III, P=0.0001* II vs III, P=0.331		
-Anti nuclear antibody (U/ml):			
Range Mean±SD	1.4-2.3 1.82±0.27	16.5-275.2 62.22±60.71	3.2-188 40.3±42.83
F value P	8.91 0.0003*		
Scheffe test P	I vs II, P=0.0003* I vs III, P=0.001* II vs III, P=0.04*		

*Significant (P<0.05).

Table (3) documents contrast among the studied groups regarding specific laboratory investigations results. Anti-DNA antibody titre ranges from {144-175, 230-370, 150-235 (IU/ml)} with a mean value of {156.80±9.66, 299.37±44.3, 194.17±27.65} in control group (I), clinically active SLE group (II) and clinically non- active SLE group (III) respectively. A statistically significant increase of anti-DNA antibody titre in active SLE group was found in contrast with the control group, P=0.0001, and a significant increase of anti-ds DNA antibody titre in non-active SLE group was found in contrast with the control group, P=0.0001 and a significant increase of anti-ds DNA antibody in the active SLE group was found in comparison to non- active SLE group, P=0.0001.

C3 ranged from {144-175, 12-43, 62-90 (mg/dl)} with a mean value of {156.80±9.66, 27.03±9.49, 74.83±8.51} in control group (I), clinically active SLE group (II) and clinically non-active SLE group (III) respectively. Concerning the complement C3, statistically significant decrease was detected in the active SLE group in comparison to the control group, P=0.0001, and a significant decline of complement C3 in non-active SLE group was found in comparison to control group, P=0.0001 and a significant decline of complement C3 in active

SLE group was found in comparison to non- active SLE group, P=0.0001.
C4 ranged from {33-50, 5-12, 6-13(mg/dl)} with a mean value of {39.73±5.16, 8.17±2.15, 9.29±2.14} in control group (I), clinically active SLE group (II) and clinically non-active SLE group (III) respectively. We have also detected a statistically significant decrease of C4 in active SLE group was found in comparison to the control group, p =0.0001, also a statistically significant decrease in C4 in non- active SLE group was found in contrast with the control group, P=0.0001 but no significant variation was found among both the active and non – active SLE groups, P= 0.331.
Anti-nuclear antibody titre (ANA) ranged from {1.4-2.3, 16.5-275.2, 3.2-188 (U/ml)} with a mean value of {1.82±0.27, 62.22±60.71, 40.3±42.83} in control group (I), clinically active SLE group (II) and clinically non- active SLE group (III) respectively. Concerning ANA titre, we detected a statistically significant increase in the active SLE group in comparison to the control group, P=0.0003, also a significant increase of ANA titre in non-active SLE group was found in contrast with the control group, P=0.001 and a significant increase of ANA in active SLE group was found in comparison to non- active SLE group, P=0.04.

Table (4): Serum adenosine deaminase level among the studied groups

Variables	The studied subjects (n=85)		
	Control group (n=15) (I)	Patients with clinically active SLE (n=35) (II)	Patients with clinically non-active SLE (n=35) (III)
• Specific laboratory investigation results:			
- adenosine deaminase (IU/ml):			
Range	5-9.1	13-21	9.5-12.8
Mean±SD	6.92±1.36	16.1±2.27	10.86±1.13
F value	169.73		
P	0.0001*		
Scheffe test	I vs II, P=0.0001*		
P	I vs III, P=0.0001*		
	II vs III, P=0.0001*		

*Significant (P<0.05).

Table (4) shows comparison between the studied groups as regard to serum adenosine deaminase expression levels, it ranged from {5-9.1, 11.5-18, 9.5-13.8} with a mean value of {6.92±1.36, 16.1±2.27, 10.86±1.13} in control group (I), clinically active SLE group (II) and clinically non-active SLE group (III) respectively. Regarding serum adenosine deaminase levels, a statistically significant increase was detected in the active SLE group in contrast with the control group, P=0.0001. A significant increase in serum adenosine deaminase levels in both the active and non- active SLE groups was found in contrast with the control group, P =0.0001 and a significant rise in serum adenosine deaminase levels in the active SLE group was found in comparison to non- active SLE group, P=0.0001.

Table (5): Correlation among adenosine deaminase levels and results of laboratory investigations among the studied groups

Variables	Adenosine deaminase expression levels among the studied subjects (n=85)	
	R	P
ESR at 1st hour	0.818	0.0001*
Hb	-0.832	0.0001*
TLC	-0.078	0.48
Total platelet count	-0.407	0.0001*
Blood urea	0.77	0.0001*
Serum creatinine	0.834	0.0001*

Urine albumin / creatinine ratio	0.841	0.0001*
anti-ds DNA antibody	0.825	0.0001*
Complement C3	-0.865	0.0001*
Complement C4	-0.669	0.0001*
Anti-nuclear antibody	0.354	0.001*

*Significant (P<0.05); r=Correlation Coefficient.

Table (5): documents correlations among ADA and various results of laboratory investigations. A positive statistically significant correlation was discovered among ADA and ESR, blood urea, serum creatinine, Urine alb/creatinine ratio, anti-dsDNA antibody and ANA titre (P=0.001); while a negative correlation was found among ADA and Hb level, platelet count, complement C3and C4, (P=0.0001) but not significant to TLC (P=0.48).

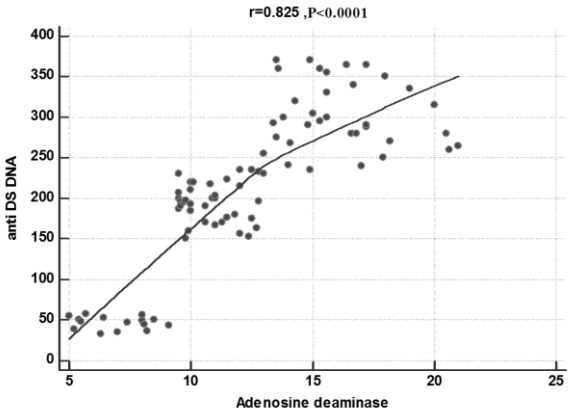

Figure (1): Correlation between ADA and anti Ds-DNA among the studied patients with SLE (clinically active and inactive) and the control group (n=85)

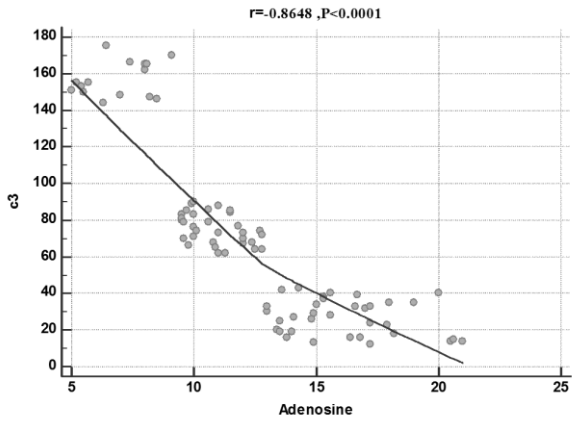

Figure (2): Correlation between ADA and complement c3 among the studied patients with SLE (clinically active and inactive) and the control group (n=85)

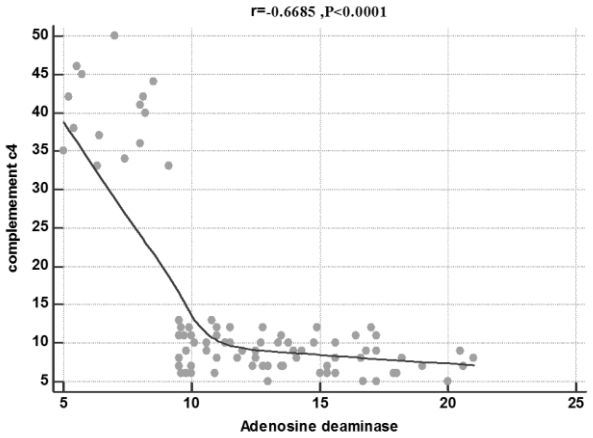

Figure (3): Correlation between ADA and complement c4 among the studied patients with SLE (clinically active and inactive) and the control group (n=85)

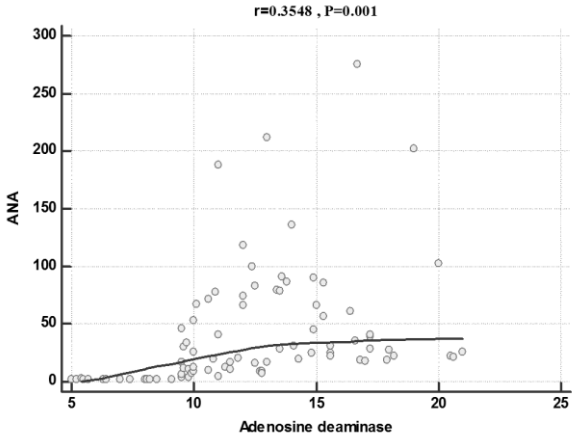

Figure (4): Correlation between ADA and ANA among the studied patients with SLE (clinically active and inactive) and the control group (n=85)

Discussion:

In the present study as regard to CBC findings, a statistically significant decline in Hb concentration at both the active and non-active SLE groups was found in comparison to control group, furthermore, a statistically significant decrease of Hb in the active SLE group when compared to non-active SLE group, P=0.0001.

As regard to TLC, a statistically significant decrease of TLC in active SLE group was found

in contrast with the control group, P=0.047 while no significant variation was detected among either the non-active SLE group and control group, P=0.923 or the active SLE group and non-active SLE group, P=0.064.

As regard to platelet's count, a statistically significant decrease of platelet count in both the active SLE group and non –active when contrasted with the control group, P=0.0001 while no significant variance was detected among active SLE group and non -active SLE group, P=0.339.

In agreement with the present study **Delgado and Guillermo, (2016)** [7] reported a significant decline in hemoglobin of active SLE patients group when contrasted with those of inactive SLE patients' group, while no significant variation in groups as regard to TLC and platelets count.

Abira et al., (2018) [8] reported that hemoglobin level, WBC and platelet counts are significantly less in lupus patients when compared to the control group.

In regards to **Khanfir et al., (2013)** [9] detected no significant changes in WBC and platelet counts in SLE patients was found in contrast with the control group. This changes in results may be due to demographic variations.

The present study revealed that renal function tests (blood urea, serum creatinine, Urine albumin/creatinine ratio and) were statistically significant increased either between active SLE group Vs control group, non- active SLE group Vs the control group or active SLE group Vs non- active SLE group, P=0.0001.

Our findings agree with **Parodis et al., (2016)** [10] who discovered statistically significant increase of serum creatinine in active SLE patients group in contrast with the non- active SLE patients group. Also, **Laurence et al., (2016)** [11] found significant elevation of serum creatinine in active lupus nephritis patients group.

The current study's results agreed with **Misra and Gupta, (2015)** [12] who reported significant elevation of A/C ratio in active Lupus Nephritis patients group.

In the present study as regard to anti-ds DNA antibody titre, a statistically significant increase in both active SLE group and non-active SLE group was found in comparison to control group, also a significant increase of anti-ds DNA antibody levels in active SLE group was found in comparison to non- active SLE group, P=0.0001.

These results are similar to **Parodis et al., (2016)** [10] who reported statistically significant elevation of anti-ds DNA levels in active SLE patients group when contrasted with non-active SLE patients group. Also, **Laurence et al., (2016)** [11] reported that anti-ds DNA levels are significantly elevated in the active lupus nephritis patients group, similarly, results obtained by **Narayanan et al., (2010)** [13] who observed that anti-dsDNA levels are increased for every patient with major renal flare patients group while in non-renal flare patients group anti-dsDNA titre is elevated in just 35% of cases.

The current research discovered a statistically significant decline of complement C3 in active and non-active SLE groups when contrasted with the control group, P=0.0001, and a significant decline of complement C3 in active SLE group was found in comparison to non-active SLE group, P=0.0001.

As regard to complement C4 a significant decrease in the active and non- active SLE groups was found in contrast with the control group, p =0.0001. However, no significant variation was found among both the active and non –active SLE groups, P= 0.331.

These findings agree with **Chi et al., (2015)** [14] who discovered that C3 and C4 had significant decrease in active SLE group in comparison to healthy control group, also **Qu et al., (2019)** [15] proved statistically significant decline of C4 in SLE group in comparison to control group.

In addition to **Narayanan et al., (2010)** [13] found that 12 out of 13 (92.3%) active SLE patients suffering renal involvement witnessed low C3 levels, and 11 have also shown low C4

levels.

The current research discovered a statistically significant elevation of ANA titre in active SLE group in comparison to the control group, P=0.0003, also a significant elevation of ANA titre in non-active SLE group was found in contrast with the control group, P=0.001 and a significant increase of ANA in active SLE group in comparison to the non- active SLE group, P=0.04.

These results are similar to **Qu et al., (2019)** [15] who reported statistically significant elevation of ANA titre in active SLE when contrasted with non-active SLE. Also, **Kumar and Bhatia, (2014)** [16] denoted that a statistically significant increase of ANA titre in active SLE group was found in comparison to non-active SLE group.

In the immunological system, ADA plays a significant function. The accumulation of proofs demonstrated its significant impact on immune reactions' function, development and maintenance. The key pathogenetic component of autoimmune conditions was deemed deficient immunological tolerance. Many studies revealed that elevated ADA activity is related to various autoimmune diseases, like rheumatoid arthritis (RA), adult-onset Still's disease and SLE**.** [5]

In contrast to the control group (P = 0,0001), the main findings of the study showed a statistically significant rise of serum adenosine deaminase activity in active and non-active SLE groups and a significant increase of serum adenosine deaminase in active SLE groups in contrast with the non-active SLE group (P = 0,0001).

These findings agree with **Gao et al., (2018)** [5] who reported that, there was significant increased serum ADA activity in active SLE patients group in comparison to non-active SLE group as well as significant rise of serum ADA activity in active and non-active SLE groups compared to control group. Also, **Saghiri et al., (2012)** [17], observed also a significant rise in serum ADA activity in SLE patients group.

Even though, these results differed from the findings of **Xun et al**., **(2013)** [18], who revealed that no significant variations were found in ADA activity between SLE patients and healthy controls. These contradictory findings may be caused by the less healthy patients in this study's control group.

The current research found a positive statistically significant correlation among adenosine deaminase and ESR, blood urea, serum creatinine, Urine albumin/creatinine ratio, anti-dsDNA antibody and anti-nuclear antibody titre (P=0.001); while it has also discovered a negative correlation among adenosine deaminase and Hb levels, total platelet count, complement C3and complement C4, (P=0.0001), yet no significant correlation among ADA and TLC was found (P=0.48).

Results of the present work were similar to results obtained by **Gao et al., (2018)** [5] who found the existence of a positive significant correlation levels among ADA activity level and titre of both ANA and anti-dsDNA antibody besides negative correlation among ADA activity levels and levels of both complement C3 and C4.

These findings agree with **Saghiri et al., (2012)** [17] who showed evidences on the substantially higher total ADA activity of SLE patients has been linked with the higher levels of ADA and the usage of ADA as a useful diagnostical marker in evaluating activity and severity of SLE illness.

However, these results contrast with **Isabella et al., (2005)** [19] who found no correlation among serum ADA and SLEDAI score. Hence, ADA can't be considered a marker for SLE activity. The explanation may be due to variations in the studied groups or the deficiency of standardizing the ADA measurement methods.

Recommendations:

- Based on the current research's findings, it's recommended to introduce ADA as a diagnostic biomarker for SLE activity.
- It's desirable to validate the current study's findings on a bigger number of patients due to the small sample size, possibly through a multicenter study.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

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